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The Patent Office
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Dated 7 March 2000

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# Request for grant of a patent

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The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — N.75979 PEJ/apt

2. Patent *(The Pat* — **9904523.9** — 26 FEB 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ISIS INNOVATION LIMITED
2 South Parks Road
Oxford OX1 3UB

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

3998564001

4. Title of the invention — PLATINUM (II) COMPOUNDS

5. Name of your agent *(if you have one)*

J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

14 SOUTH SQUARE
GRAY'S INN
LONDON WC1R 5LX

26001

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer "Yes" if:*

*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body:*
*See note (d))*

Yes

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| Continuation sheets of this form | - |
| Description | 31 |
| Claim(s) | 4 |
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10. If you are also filing any of the following, state how many against each item.

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|---|---|
| Priority documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | |
| Request for preliminary examination and search *(Patents Form 9/77)* | 1 |
| Request for substantive examination *(Patents Form 10/77)* | |
| Any other documents *(please specify)* | |

11. I/We request the grant of a patent on the basis of this application

Signature [signature] Date 26 February 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

P G A ELLIS-JONES
0171 405 3292

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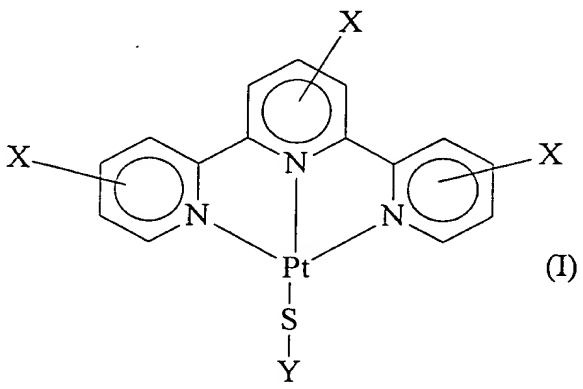
# PLATINUM (II) COMPOUNDS

The present invention relates to platinum (II) compounds for use in the treatment of the human or animal body. The invention in particular relates to 2,2':6',2"-terpyridine platinum (II) compounds for use as anti-protozoal, anti-rheumatoid arthritic or anti-tumour agents.

In a first aspect the present invention provides a compound which is a complex of formula (I)




(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

The term "alkyl" as used herein includes both unsubstituted and substituted, straight and branched chain radicals. Typically it is $C_1$ - $C_6$ alkyl, preferably $C_1$ - $C_4$ alkyl, for example methyl, ethyl, i-propyl, n-propyl, t-butyl, s-butyl or n-butyl. It may also be pentyl, hexyl and the various branched chain isomers thereof. When the alkyl group is substituted it typically bears one or more substituents selected from aryl, cycloalkyl, halogen, trihaloalkyl such as trifluoromethyl, hydroxy, alkoxy, aralkoxyl, amino, mono or dialkylamino, carbonyl and carboxy.

The term "cycloalkyl" as used herein typically means a cycloalkyl group having 3 to 8 carbons, for example cyclopropyl and cyclooctyl. A cycloalkyl group may be unsubstituted or substituted as the alkyl groups above.

The term "alkenyl" as used herein includes unsubstituted and substituted, straight and branched chain radicals having one or more double bonds. Typically it is $C_2$ - $C_6$ alkenyl such as, for example, allyl, butenyl, butadienyl, pentenyl or hexenyl. When the alkenyl group is substituted it typically bears one or more substituents as defined above for the alkyl groups.

The term "cycloalkenyl" as used herein typically means a cycloalkenyl group having 4 to 8 carbons, for example cyclopentenyl or cyclooctadiene.

The term "alkynyl" as used herein includes unsubstituted and substituted, straight and branched chain radicals having one or more triple bonds. Typically it is $C_2$ - $C_6$ alkynyl, such as butynyl. When the alkynyl group is substituted it typically bears one or more substituents as defined above for the alkyl groups.

The term "aryl" as used herein includes both monocyclic and bicyclic aromatic groups which typically contain from 6 to 10 carbons in the ring portion, such as phenyl or naphthyl. The aryl group is unsubstituted or substituted. When it is substituted the aryl group may be substituted by one or more substituents selected from $C_1$-$C_6$, alkyl, $C_1$-$C_6$ alkoxyl, trihaloalkyl such as trifluoromethyl, halogen and hydroxy.

The term "heterocyclyl" as used herein is typically a 3- to 7-membered, saturated or unsaturated heterocyclic ring containing at least one heteroatom selected

from N, O and S and which is optionally fused to a second 5- or 6-membered, saturated or unsaturated heterocyclic ring or to an aryl group as defined above. The heterocyclic ring may be, for example, pyridine, furan, thiophene, pyrrole, pyrimidine, pyrazine, pyridazine, pyrazole or indazole, or a cyclic ether such as glucose.

The term "aralkyl" as used herein refers to alkyl groups as previously defined having an aryl substituent, for example benzyl, phenethyl, diphenylmethyl and triphenylmethyl.

The term "alkaryl" as used herein refers to aryl groups as previously defined having an alkyl substituent.

The term "acyl" as employed herein includes alkyl, aryl and heterocyclyl as described above linked to a carbonyl group.

The term "halogen" as used herein means fluorine, chlorine, bromine and iodine.

The term "alkoxyl" or "aralkoxyl" as used herein includes any of the above alkyl, cycloalkyl or aralkyl groups linked to an oxygen atom.

In accordance with the conventional nomenclature for terpyridine ring systems simple numbering is used for the left hand ring of the terpyridine in formula (I), numbering qualified by prime (') is used for the central ring and numbering qualified by double prime (") is used for the right hand ring.

X is preferably hydrogen, halogen such as chlorine or alkoxyl such as methoxyl, ethoxyl or propoxyl, preferably ethoxyl. A substituent may preferably be at the 4' position of the terpyridine system.

Y may be substituted with one or more electron withdrawing groups such as a halogen, hydroxyl, carbonyl, amide or carboxyl and/or one or more electron donating groups. Y is preferably alkyl, for example, $(CH_2)_nOH$ or $(CH_2)_n NH_3^+$ wherein n is an integer of 1 to 6; aralkyl, for example aryl$CH_2$ such as benzyl; heterocyclyl , for example, a 5- or 6-membered saturated heterocyclic ring such as a deoxy-glucose, for instance deoxy-$\beta$-D-glucose or deoxy-glucose substituted by one or more groups such as acyl groups, or a 5- or 6-membered unsaturated heterocyclic ring containing at least one N which may be fused to a 6-membered aryl ring, for example, pyridyl

such as 2-pyridyl or 4-pyridyl, pyrimidyl such as 2-pyrimidyl, imidazolyl such as 2-imidazolyl, or benzimidazolyl such as 2-benzimidazoyl; or an inorganic oxyacid or inorganic oxyacid derivative such as $SO_3R$ or $PO_3R_2$ wherein R is hydrogen or alkyl. In one embodiment n is an integer of at least 3.

Preferred complexes of formula (I) are those wherein:

X is hydrogen, halogen such as chlorine or alkoxyl such as methoxyl, ethoxyl or propoxyl, preferably ethoxyl; and

Y is alkyl, for example, $(CH_2)_nOH$ or $(CH_2)_n NH_3^+$ wherein n is an integer of 1 to 6; aralkyl, for example aryl$CH_2$ such as benzyl; heterocyclyl, for example, a 5- or 6-membered saturated heterocyclic ring such as a deoxy-glucose, for instance deoxy-$\beta$-D-glucose or deoxy-glucose substituted by one or more groups such as acyl groups. or a 5- or 6-membered unsaturated heterocyclic ring containing at least one N which may be fused to a 6-membered aryl ring, for example, pyridyl such as 2-pyridyl or 4-pyridyl, pyrimidyl such as 2-pyrimidyl, imidazolyl such as 2-imidazolyl, or benzimidazolyl such as 2-benzimidazoyl; or an inorganic oxyacid or inorganic oxyacid derivative such as $SO_3R$ or $PO_3R_2$ wherein R is hydrogen or alkyl.

More preferred complexes of formula (I) are:

2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

2-aminoethanethiolate-(2,2':6',2"-terpyridine)platinum (II),

pyridine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),

pyridine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

pyridine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

pyridine-4-thiolate-(2,2':6',2"-terpyridine)platinum (II),

pyridine-4-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

pyridine-4-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

pyrimidine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),

pyrimidine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

pyrimidine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

imidazole-2-thiolate-bis(2,2':6',2"-terpyridine)platinum (II),

imidazole-2-thiolate-bis(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
imidazole-2-thiolate-bis(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
benzimidazole-2-thiolate-bis(2,2':6',2"-terpyridine)platinum (II),
benzimidazole-2-thiolate-bis(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
benzimidazole-2-thiolate-bis(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II), and
1-thio-$\beta$-D-glucose(2,2':6',2"-terpyridine)platinum (II).

The complexes of formula (I) may be negatively charged, neutral or positively charged. It will be appreciated that Y may be selected to obtain the desired overall charge. For example, when Y is $PO_3^{2-}$ the overall charge on the compound of formula (I) is -1, when Y is $(PO_3R^1)^-$ wherein $R^1$ is for example $C_1$ to $C_6$ alkyl, the compound of formula (I) is neutral and when Y is $PO_3(R^1)_2$ wherein R is as defined above, the overall charge on the compound of formula (I) is +1. Compounds of formula (I) which are neutral overall may be able to pass through cell membranes more rapidly.

The present invention also includes the salts of the complexes of formula (I). When the complexes of formula (I) are positively or negatively charged a counterion is present. The counterions are physiologically tolerable counterions and are generally selected to obtain good water solubility. Counterions which may suitably be used include sulphate, sulphonate, phosphate, pyrophosphate, phosphate esters and diesters, phosphonate, carbonate, carboxylate and any other non-toxic counterions which retains an appropriate level of solubility with the platinum (II) compound. Stable conjugates with anionic polymers or dendrimers may also be used and may be particularly appropriate for the delivery of the compounds of formula (I) to tumour cells because of the "enhanced cell permeability and retention effect" (EPR) of tumour cells.

The biological activity of the compounds of formula (I) may be affected by the leaving ability of the thiolate ligand which is linked to the pKa of the thiol Y-SH. Generally the pKa of the thiol is not more than 11. In one embodiment the pKa of the thiol is greater than 6.

The present invention includes all possible isomers of the compounds of formula (I) and mixtures thereof, including diastereomeric mixtures and racemic

mixtures, resulting from the possible combinations of (*R*) and (*S*) stereochemistry when stereogenic centres are present.

The compounds of formula (I) may be prepared by methods known in the art. For example, the compounds of formula (I) may be prepared from chloro(2,2':6',2"-terpyridine)platinum (II) chloride by treatment with a thiol Y-SH, in one instance the chloro(2,2':6',2"-terpyridine)platinum (II) chloride may be converted to a suitable salt before treatment with the thiol. The compounds of formula (I) may also be prepared from a complex formed from reacting a platinum complex of 1,5-cyclooctadiene with a 2,2':6',2"-terpyridine (see, for example, WO97/27202).

2-Hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II), in particular, shows a wide range of activities against protozoal parasites. It is effective against *Leishmania donovani, Trypanosoma cruzi* and *Trypanosoma brucei*. In addition 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II) has been shown to irreversibly inactivate the reduced form of human thioredoxin reductase and may therefore have potential as a therapeutic agent for rheumatoid arthritis. It has also been found to have anti-tumour activity against a range of human ovarian tumour cell lines.

Accordingly a human or animal may be treated by administering thereto a non-toxic and therapeutically effective amount of a compound which is a complex of formula (I). The condition of the human or animal may thereby be ameliorated. Protozoal infection, rheumatoid arthritis or tumours can thus be treated.

In another aspect the present invention provides use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an anti-protozoal, anti-rheumatoid arthritic or anti-tumour agent.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as active ingredient, in association with a pharmaceutically acceptable carrier, excipient or other additive, if necessary.

The pharmaceutical composition containing a compound of formula (I) or salts thereof may be prepared in a conventional way by employing conventional non-

toxic pharmaceutical carriers or diluents in a variety of dosage forms and ways of administration.

In particular, the compounds of formula (I) can be administered:

A) orally, for example, as tablets, troches, lozenges, aqueous or oily suspension, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such composition may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring and preserving agents in order to provide elegant and palatable preparations.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example maize starch or alginic acid; binding agents, for example maize starch, gelatin or acacia, and lubricating agents, for example magnesium stearate or stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such glyceryl monostearate or glyceryl distearate may be employed. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example

polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxyacetamol, or condensation products of ethylene oxide with partial esters derived from fatty acids and an hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol anhydrides, for example polyoxysorbitan monooleate.

The said aqueous suspension may also contain one or more preservatives, for example ethyl or n-propyl *p*-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, one or more sweetening agents such as sucrose or saccharin.

An oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil, coconut oil or in a mineral oil such as liquid paraffin. The oily suspension may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation.

These compositions may be preserved by the addition of an antioxidant such as ascorbic acid. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions.

The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these.

Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate.

The emulsions may also contain sweetening and flavouring agents. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, colouring and flavouring agents.

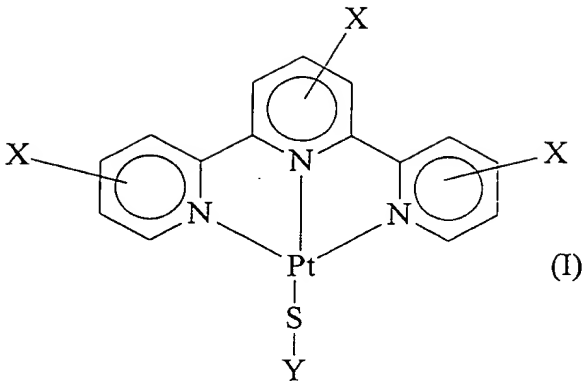
B) parenterally, either subcutaneously or intravenously or intramuscularly, or intrasternally, or by infusion techniques. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or olagenous suspensions.

These suspensions may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium.

For this purpose any bland fixed oils may be conventionally employed including synthetic mono or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables.

The daily dose varies according to the activity of the specific compound, the age, weight, and conditions of the subject to be treated, the type and the severity of the disease, and the frequency and route of administration. Typically the daily dose is from 0.1 to 50 mg per kg of body weight. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration may contain from 5 to 95% of the total composition. Dosage unit forms will generally contain between from 5 to 500 mg of the active compound.

In a further aspect the present invention provides a compound which is a complex of formula (I)




(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, with the proviso that the complex of formula (I) is not 2-hydroxyethanethiolate(2,2':6',2"-terpyridine)platinum (II) or 2-aminoethanethiolate(2,2':6',2"-terpyridine)platinum (II).

The Examples which follow further illustrate the present invention.

**Examples**

***General procedures***

Solvents (A.R. and h.p.l.c. grade) were purchased from Aldrich Chemical

Company and Rathburn Chemicals. Diethylamine was dried over potassium hydroxide pellets, distilled from potassium hydroxide and stored under argon over potassium hydroxide pellets. Water refers to deionised water.

Melting points were determined on a Reichert heating stage and are uncorrected.

$^1$H n.m.r. spectra were recorded on a Varian Gemini 200MHz spectrometer or a Bruker AM 500 MHz spectrometer at 300K. Samples run in deuterochloroform ($CDCl_3$) were referenced to the solvent (7.26 ppm). Samples run in deuterium oxide ($D_2O$) were referenced to dioxane (3.75 ppm). Samples run in deuterated dimethylsulfoxide (DMSO) were referenced to the solvent (2.50 ppm). Chemical shifts are expressed in ppm. Abbreviations for multiplicity are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet; br d, broad doublet. Relative intensities are expressed as the number of protons such that "2H" denotes a relative intensity of two protons. $^1$H n.m.r. spectra are expressed in order of chemical shift, multiplicity, coupling constant, relative intensity and assignment.

Flash chromatography was performed by using h.p.l.c. grade solvents and Merck silica gel 60 (230-400 mesh ASTM). Thin layer chromatography was performed on Merck precoated aluminium t.l.c. plates coated with silica gel 60F 254 (0.2 mm) and visualised by means of ultraviolet light.

Electrospray mass spectroscopy was carried out on a VG Biotech Bio-Q spectrometer using a dilute solution of the sample in methanol/water.

***Antiparasitic Activity***

SCREEN 1 -PROTOCOL 1

*Leishmania donovani* (strain MHOM/ET/67/L82) amastigotes, derived from the spleen of a golden hamster (Wright's strain) were used to infect mouse peritoneal macrophages from CD1 (Charles River Ltd., Margate, UK) mice at a parasite: macrophage ratio of 10:1. Infected macrophages were maintained in RPMI 1640 medium plus 10% heat inactivated fetal calf serum (hiFCS) (Harlan Sera-Lab., Crawley, UK) in 16-well Labtek chamber slides (Nunc Inc., IL, USA) at 37°C in 5%

$CO_2$/air mixture. Infected cultures were exposed to test compounds in medium, in a three-fold dilution series from 30 $\mu$M with quadruplicate cultures at each concentration for 5 days, with medium + drug replaced once during the period. Sodium stilbogluconate (Glaxo Wellcome, UK) was included in the assays as the positive control and had an $ED_{50}$ = 10.4 $\mu$g of Sb/mL (Mr of the drug is unknown) Activity was determined, after cultures had been methanol fixed and Giemsa stained, from the proportion of infected cells in treated and untreated cultures and dose response curves analysed by linear regression to obtain an $ED_{50}$ value where possible.

*Trypanosoma cruzi* (strain MHOM/BR/00/Y) trypomastigotes derived from MDCK fibroblasts were used to infect mouse peritoneal macrophages from CD1 mice at a parasite: macrophage ratio of 5:1. Infected cells were maintained in RPMI 1640 medium plus 10% hiFCS in 16-well Labtek chamber slides at 37°C in 5% $CO_2$/air mixture. Infected cultures were exposed to test compounds in medium, in a three-fold dilution series from 30 $\mu$M with quadruplicate cultures at each concentration for 3 days. Nifurtimox (Bayer, Germany) was used as the positive control and had an $ED_{50}$ in the range 2.2-4.4 $\mu$M. Activity was determined, after cultures had been methanol fixed and Giemsa stained, from the proportion of infected cells in treated and untreated cultures and dose response curves analysed by linear regression to obtain an $ED_{50}$ value where possible.

*Trypanosoma brucei brucei* (strain S427) bloodstream trypomastigotes were cultured in HMI-18 medium containing 20% hiFCS at 37°C in 5% $CO_2$/air mixture. Trypomastigotes were exposed to test compounds in medium, in a three-fold drug dilution series from 30 $\mu$M with triplicate culures at each concentration for 72 hours. Pentamidine (Rhone Poulenc Rorer Ltd., Dagenham, UK) was used as the positive control and had an $ED_{50}$ of 0.03-0.1$\mu$M. Drug activity was determined by using an MTT-based cytotoxicity assay and dose response curves analysed by linear regression to obtain an $ED_{50}$ value where possible.

SCREEN 2 - PROTOCOL II

The assays follow those outlined in Screen 1- Protocol 1 but include a range of doses in a dilution series from 30$\mu$M. Dose response curves were analysed by linear regression and $ED_{50}$ values determined.*T. brucei* numbers/ml are determined using a Coulter Counter.

*Leishmania donovani: in vivo* protocol.

Day 0 — 8 - 10 week old (18-20g) female BALB/C mice are infected with 2 x 107 *L. donovani* HU3 amastigotes, freshly harvested from the spleen of an infected Golden hamster. The inoculum is administered i.v. (lateral tail vein).

Day 7 — 1 mouse is sacrificed to check for patency of infection. An impression smear of the liver is made, Giemsa stained and examined. There should ideally be 1 amastigotes per nuclei (count 500 nuclei) This indicates a good, exponential infection. A group weight is measured. Commence dosing. Usual regimen is for 5 consecutive days.

Positive control mice are given Pentostam s.c. x 5 days - 45, 15 and 5 mgSbV/kg.

Day 14 — All mice are weighed and necropsied. Livers are dissected and weighed. Impression smears are made, fixed and Giemsa stained for microscopical examination. The number of amastigotes per 500 nuclei is counted. This figure is then multiplied by the weight of the organ (mg). % inhibition compared with untreated control is

calculated. In a dose-response experiment the $ED_{50}$ is calculated by linear regression analysis (xlfit). The difference in group weight can give an indication of toxicity but this is often obvious.

***Inhibition of Trypanothione Reductase from Trypanosoma cruzi***

The assay solution contains NADPH (100$\mu$M), trypanothione disulphide (100$\mu$M) and trypanothione reductase (3nM) in buffer at pH 7.5. The hydroxyethanethiolate complex (**1**) (40$\mu$M) leads to 95% irreversible inhibition of the enzyme within 20 min. If the NADPH is left out of the assay solution, (**1**) is a reversible competitive inhibitor with $K_i$= 60$\mu$M. The irreversibly inactivated enzyme (formed in the presence of NADPH) is stable to dialysis, whereas the reversibly inhibited enzyme (in the absence of NADPH) is completely reversed on dialysis.

The hydroxyethanethiolate complex (**1**) (40$\mu$M) is not an irreversible inactivator of human glutathione reductase either in the presence or absence of NADPH.

***Inhibition of HumanThioredoxin Reductase***

The inhibition of human thioredoxin reductase were undertaken using the DTNB [5,5'-dithiobis-(2-nitrobenzoate)] assay (S. Gromer *et al.*, *J. Biol. Chem.*, **1998**, *273*, 20096-20101.) The 2,2':6',2"-terpyridine Pt(II) complexes, (**1**) , (**2**), (**3**) and (**4**), at 20$\mu$M concentration, each irreversibly inhibited the enzyme completely within 10 min. in the presence of NADPH.

***Antitumour Activity***

The thiolato-2,2':6',2"-terpyridine Pt(II) complex, 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II), (**1**) was evaluated for *in vitro* cytotoxicity against five human ovarian carcinoma cell lines which included two selected for resistance to cisplatin ($CHlcis^R$ and $A2780cis^R$) and one for resistance to doxorubicin ($CHldox^R$). The compound was exposed to cells for 96 h and growth inhibition assessed using the sulforhodamine B protein staining assay. The $IC_{50}$ values (in $\mu$M) are shown in Table 2. Carboplatin is included for comparison.

*Synthesis of 2,2':6',2"-Terpyridine Platinum (II) Complexes*

By way of example the synthesis and characterisation of the several thiolate-2,2':6',2"-terpyridine platinum (II)] complexes are provided. The platination of 2,2':6',2"-terpyridine and 4'-chloro-2,2':6',2"-terpyridine was achieved as previously described (WO97/27202 and *J.Chem. Res.*, **1996**, 386-387).

2-Hydroxyethanethiolate-(2,2':6',2"-terpyridine) platinum (II) nitrate **(1)** was prepared by the following general method which is more effective and reliable than the literature method. (K. Jennette *et al.*, *Proc. Natl. Acad. Sci. USA*, **1974**, *71*, 3839-3843).

Silver nitrate (35.7mg, 0.21mmol) was dissolved in aqueous acetone (4: 1 acetone: water, 0.5ml) and added to a suspension of diiodo-1,5-cylooctadienyl platinum (I) (55.7mg, 0.1mmol) in aqueous acetone (0.75ml). The mixture was vigourously shaken until the dark yellow colour had subsided then the precipitated silver salt isolated by centrifugation and discarded. The supernatant containing the active platinum species was added to a suspension of 2,2':6',2"-terpyridine (0.08mmol, 18.7mg) in acetonitrile (0.25ml). After standing for *ca.* 5 min. the yellow precipitate formed was isolated by centrifugation, washed with ether: acetonitrile (3: 1, 3x1.5ml) then redissolved in demineralised water (1ml). To this solution was added mercaptoethanol (7.54µl = 8.6mg, 0.11mmol). After standing for 1 hour the product was isolated by precipitation from excess acetone: ether (5: 3, 40ml), washed with acetone: ether then ether alone and dried in a vacuum dessicator.

The product was a brick-red powdery solid (35.9mg, 79.1%).

Electrospray mass spectrum and 500MHz proton nmr precisely matched that from material made *via* the literature method from $[Pt(Terpy)Cl]^+.Cl^-$.

**2-Hydroxyethanethiolate-(4'-chloro-2,2':6',2"-terpyridine) platinum (II) nitrate (2)**

4'-Chloro-2,2':6',2"-terpyridine is commercially available from

Aldrich Chemical Co., UK or Lancaster, UK. The preparation of the title compound was by the general method given above.

The product was a dark red powdery solid (23.5mg, 48.8%).

m/z (ESI+, *ex.* MeOH: $H_2O$): 540 ($M^+$); $\delta_H$ (500MHz, $D_2O$, referenced to dioxan (3.75ppm)/ ppm: 9.03 (2H, d, *J* 5.3 Hz, broadened, H6,6"), 8.37 (2H, s, H3'/5'), 8.34 (2H, td, *J* 7.9, 1.3Hz, H4,4"), 8.14 (2H, d, *J* 7.8Hz, H3,3"), 7.79 (2H, m, H5,5"), 3.67 (2H, t, *J* 6.9Hz, $OCH_2CH_2S$), 2.56 (2H, t, *J* 6.8Hz, $OCH_2CH_2S$).

**2-Hydroxyethanethiolate-(4'-ethoxy-2,2':6',2"-terpyridine) platinum (II) nitrate (3)**

4'-Ethoxy-2,2':6',2"-terpyridine was prepared in excellent yield by ethanolysis of 4'-chloro-2.2':6'.2"-terpyridine activated by $FeCl_2.4H_2O$ or by reaction with sodium ethoxide without activation, m.p. 85-86°C. TLC (alumina, petroleum ether 40-60°C / EtOAc 3 / 1) : $R_f$ = 0.59. $\delta_H$ (200 MHz, $CDCl_3$) : 8.70 (*d*, $^3J(6,5)$ = 4.1, 2H, H-C(6), H-C(6")); 8.63 (*d*, $^3J(3,4)$=8.1, 2H, H-C(3) , H-C(3")); 8.02 (*s*, 2H, H-C(3'), H-C(5')); 7.86 (*dt*, $^4J(4,6)$ = 1.8, $^3J(4,3)$ = $^3J(4,5)$ = 7.3, 2H, H-C(4), H-C(4")); 7.34 (*ddd*, $^4J(5,3)$ = 1.2, $^3J(5,6)$ = 4.8, $^3J(5,4)$ = 7.5, 2H, H-C(5), H-C(5")); 4.32 (*q*, 2H, $^3J_{vic}$ = 7.1, 2H, $\underline{H}_2$-COterpy); 1.50 (*t*, $^3J_{vic}$ = 6.9,$\underline{H}_3$-$CCH_2$). m/z (ESI) : 278 ($MH^+$).

4'-Ethoxy-2,2':6',2"-terpyridine (0.08mmol, 22.2mg) were used in the general method described above to give the title product as a dark red powdery solid (26.9mg, 55.0%).

m/z (ESI+, *ex.* MeOH: $H_2O$): 549 ($M^+$); $\delta_H$ (500MHz, $D_2O$, referenced to dioxan (3.75ppm)/ ppm: 8.96 (2H, d, *J* 5.1 Hz, broadened, H6,6"), 8.23 (2H, t, *J* 7.3Hz, H4,4"), 8.03 (2H, d, *J* 7.9Hz, H3,3"), 7.69 (2H, m, H5,5"), 7.60 (2H, s, H3'/5'), 4.30 (2H, q, J 7.0Hz, $OCH_2CH_3$), 3.68 (2H, t, *J* 6.9Hz, $OCH_2CH_2S$), 2.53 (2H, s, broadened, $OCH_2CH_2S$), 1.53 (3H, t, J 6.5Hz, $OCH_2CH_3$).

**Pyridine-4-thiolate(2,2':6',2"-terpyridine)platinum(II) nitrate**

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water

(4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 4-mercaptopyridine (13.3 mg, 0.12 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 4-mercaptopyridine (2,2':6',2"-terpyridine)platinum(II) nitrate (40 mg, 83%) as a orange solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^1$H n.m.r. {400 MHz, $D_2O$}: $\partial$ 8.75, d, $J$=5.4 Hz, 2H, H6, H6"; 8.48, t, $J$=8.1 Hz, 1H, H4'; 8.36-8.29, m, 4H, H4, H4", H3', H5'; 8.24, d, $J$=7.8 Hz, 2H, H3, H3"; 7.99, AA'BB'm, 4H, H2"', H3"', H5"', H6"'; 7.63, m, 2H, H5, H5".

**Pyridine-4-thiolate(4'-chloro-2,2':6',2''-terpyridine)platinum(II) nitrate**

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (21.4 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 4-mercaptopyridine (13.3 mg, 0.12 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The

mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 4-mercaptopyridine (4'-chloro-2,2':6',2"-terpyridine)platinum(II) nitrate (45 mg, 89%) as a orange-brown solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^1$H n.m.r. {400 MHz, $D_2O$}: $\partial$ 8.83, d, *J*=5.5 Hz, 2H, H6, H6"; 8.55, s, 2H, H3', H5'; 8.39, apparent t, *J*=7.9 Hz, 2H, H4, H4"; 8.28, d, *J*=7.7 Hz, 2H, H3, H3"; 8.00, AA'BB'm, 4H, H2"', H3"', H5"', H6"'; 7.71, m, 2H, H5, H5".

**Pyridine-2-thiolate(2,2':6',2''-terpyridine)platinum(II) nitrate**

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptopyridine (15 mg, 0.13 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptopyridine (2,2':6',2"-terpyridine)platinum(II) nitrate (42 mg, 88%) as a yellow solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml).

**Pyridine-2-thiolate(4'-chloro-2,2':6',2''-terpyridine)platinum(II) nitrate**

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1,

0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptopyridine (15 mg, 0.13 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptopyridine (4'-chloro-2,2':6',2"-terpyridine)platinum(II) nitrate (42 mg, 82%) as a yellow solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml).

**Imidazole-2-thiolate-bis(2,2':6',2''-terpyridine)platinum(II) dinitrate**

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (33.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptoimidazole (6.01 mg, 0.060 mmol) in water (3 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptoimidazole bis[(2,2':6',2"-terpyridine)platinum(II)] dinitrate (57 mg, 88%) as a crimson solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^{1}$H n.m.r.

{400 MHz, $D_2O$}: ∂ 8.72, d, *J*=5.5 Hz, 2H, H6, H6"; 8.44, t, *J*=8.2 Hz, 2H, 2xH4'; 8.30-8.27, m, 4H, 2xH4, 2xH4"; 8.10, d, *J*=8.2 Hz, 2H, H3', H5'; 8.09, d, *J*=8.2 Hz, 2H, H3', H5'; 8.05, d, *J*=8.0 Hz, 2H, H3, H3"; 8.02, d, *J*=7.9 Hz, 2H, H3, H3"; 7.89, d, *J*=5.5 Hz, 2H, H6, H6"; 7.54-7.48, m, 5H, 2xH5, 2xH5", either $H_x$ or $H_y$; 7.34, d, *J*=1.8 Hz, 1H, either $H_x$ or $H_y$.

**Imidazole-2-thiolate-bis(4'chloro-2,2':6',2''-terpyridine)platinum(II) dinitrate**

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (38.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptoimidazole (6.01 mg, 0.060 mmol) in water (3 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptoimidazole bis[(4'-chloro-2,2':6',2"-terpyridine)platinum(II)] dinitrate (66 mg, 96%) as a dark purple solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^1$H n.m.r. {400 MHz, $D_2O$}: ∂ 8.78, d, *J*=5.6 Hz, 2H, H6, H6"; 8.47, s, 2H, H3', H5'; 8.46, s, 2H, H3', H5'; 8.34-8.27, m, 4H, 2xH4, 2xH4"; 8.08, d, *J*=8.3 Hz, 2H, H3, H3"; 8.05, d, *J*=8.2 Hz, 2H, H3, H3"; 7.94, d, *J*=5.6 Hz, 2H, H6, H6"; 7.60-7.54, m, 4H, 2xH5, 2xH5"; 7.51, apparent broad s, 1H, either $H_x$ or $H_y$; 7.34, apparent broad s, 1H, either $H_x$ or $H_y$.

**Benzimidazole-2-thiolate-bis(2,2':6',2''-terpyridine)platinum(II) dinitrate**

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water

(4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (33.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptobenzimidazole (9.01 mg, 0.060 mmol) in water (3 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptobenzimidazole bis[(2,2':6',2"-terpyridine)platinum(II)] dinitrate (64 mg, 94%) as a crimson solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^1$H n.m.r. {400 MHz, $D_2O$}: $\partial$ 8.86, d, *J*=4.9 Hz, 2H, H6, H6"; 8.49, t, *J*=8.2 Hz, 1H, H4'; 8.47, t, *J*=8.2 Hz, 1H, H4'; 8.27-8.22, m, 4H, 2xH4, 2xH4"; 8.15, d, *J*=8.2 Hz, 2H, H3', H5'; 8.14, d, *J*=8.2 Hz, 2H, H3', H5'; 8.08, d, *J*=7.8 Hz, 2H, H3, H3"; 8.04, d, *J*=7.8 Hz, 2H, H3, H3"; 7.77, d, *J*=4.8 Hz, 2H, H6, H6"; 7.71, d, *J*=8.2 Hz, 1H, either Hz or Hw; 7.67, d, *J*=8.2 Hz, 1H, either Hz or Hw; 7.49, m, 2H, H5, H5"; 7.45, t, *J*=7.8 Hz, 1H, either Hx or Hy; 7.36, m, 2H, H5, H5"; 7.29, t, *J*=8.1 Hz, 1H, either Hx or Hy.

**Benzimidazole-2-thiolate-bis(4'-chloro-2,2':6',2"-terpyridine)platinum(II) dinitrate**

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (38.6 mg, 0.144 mmol) in

acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptobenzimidazole (9.01 mg, 0.060 mmol) in water (3 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptobenzimidazole bis[(4'-chloro-2,2':6',2"-terpyridine)platinum(II)] dinitrate (55 mg, 77%) as a yellow-brown solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^1$H n.m.r. {400 MHz, $D_2O$}: $\partial$ 8.95, d, $J$=4.8 Hz, 2H, H6, H6"; 8.53, s, 2H, H3', H5'; 8.51, s, 2H, H3', H5'; 8.31-8.25, m, 4H, 2xH4, 2xH4"; 8.12, d, $J$=7.8 Hz, 2H, H3, H3"; 8.07, d, $J$=7.3 Hz, 2H, H3, H3"; 7.83, d, $J$=4.5 Hz, 2H, H6, H6"; 7.71, d, $J$=8.2 Hz, 1H, either Hz or Hw; 7.67, d, $J$=8.1 Hz, 1H, either Hz or Hw; 7.56, m, 2H, H5, H5"; 7.46, t, $J$=7.6 Hz, 1H, either Hx or Hy; 7.43, m, 2H, H5, H5"; 7.30, t, $J$=7.6 Hz, 1H, either Hx or Hy.

**Pyrimidine-2-thiolate (2,2':6',2''-terpyridine)platinum(II) nitrate**

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptopyrimidine (8.9 mg, 0.080 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to

yield 2-mercaptopyrimidine (2,2':6',2"-terpyridine)platinum(II) nitrate (43 mg, 90%) as a dark crimson solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^1$H n.m.r. {400 MHz, $D_2O$}: ∂ 8.75, d, *J*=5.5 Hz, 2H, H6, H6"; 8.42, t, *J*=8.1 Hz, 1H, H4'; 8.31-8.19, m, 8H, H3, H3", H4, H4", H3', H5', Hx, Hz; 7.60, apparent t, *J*=7.2 Hz, 2H, H5, H5"; 7.01, t, *J*=5.0 Hz, 1H, Hy.

**Pyrimidine-2-thiolate (4'-chloro-2,2':6',2''-terpyridine)platinum(II) nitrate**

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (21.4 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptopyrimidine (8.9 mg, 0.080 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptopyrimidine (4'-chloro-2,2':6',2"-terpyridine)platinum(II) nitrate (35.2 mg, 69%) as a dark purple solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^1$H n.m.r. {400 MHz, $D_2O$}: ∂ 8.81, d, *J*=4.8 Hz, 2H, H6, H6"; 8.49, s, 2H, H3', H5'; 8.36, apparent t, *J*=7.9 Hz, 2H, H4, H4"; 8.25, d, *J*=5.0 Hz, 2H, Hx, Hz; 8.23, d, *J*=7.8 Hz, 2H, H3, H3"; 7.68, apparent t, *J*=6.7 Hz, 2H, H5, H5"; 7.03, t, *J*=5.0 Hz, 1H, Hy.

**Purine-6-thiolate bis(2,2':6',2''-terpyridine)platinum(II) dinitrate**

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water

(4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (33.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A suspension of 6-mercaptopurine (10.2 mg, 0.060 mmol) in water (6 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 6-mercaptopurine bis[(2,2':6',2"-terpyridine)platinum(II)] dinitrate (57 mg, 84%) as a purple-brown solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^1$H n.m.r. {400 MHz, $D_2O$}: $\partial$ 9.31, s, 1H, Hy; 8.78, s, 1H, Hx; 8.73, d, *J*=5.1 Hz, 2H, H6, H6"; 8.51, t, *J*=8.1 Hz, 1H, H4'; 8.48, t, *J*=8.2 Hz, 1H, H4'; 8.32-8.25, m, 4H, 2xH4, 2xH4"; 8.19, d, *J*=8.2 Hz, 2H, H3', H5'; 8.14, d, *J*=8.2 Hz, 2H, H3', H5'; 8.11-8.07, m, 4H, 2xH3, 2xH3"; 7.89, d, *J*=4.9 Hz, 2H, H6, H6"; 7.49-7.46, m, 4H, 2xH5, 2xH5".

**Purine-6-thiolate bis(4'-chloro-2,2':6',2''-terpyridine)platinum(II) dinitrate**

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (38.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptobenzimidazole (10.2 mg, 0.060 mmol) in water (3 ml) was

added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 6-mercaptopurine bis[(4'-chloro-2,2':6',2"-terpyridine)platinum(II)] dinitrate (67.1 mg, 93%) as a crimson solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). $^1$H n.m.r. {400 MHz, $D_2O$}: $\partial$ 9.31, s, 1H, Hy; 8.79-8.77, m, 3H, Hx, H6, H6"; 8.56, s, 2H, H3', H5'; 8.52, s, 2H, H3', H5'; 8.35-8.29, m, 4H, 2xH4, 2xH4"; 8.13-8.08, m, 4H, 2xH3, 2xH3"; 7.94, d, *J*=5.0 Hz, 2H, H6, H6"; 7.57-7.48, m, 4H, 2xH5, 2xH5".

**1-Thio-β-D-glucose (2,2':6',2"-terpyridine)platinum(II) nitrate (4)**

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.0 mg, 0.102 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 1-thio-β-D-glucose (15.3 mg, 0.070 mmol) in water (2 ml) was added. The mixture was vortexed and sonicated for 45 min and then added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 1-thio-β-D-glucose (2,2':6',2"-terpyridine)platinum(II) nitrate (38 mg, 79%) as a dark purple solid. The product was purified by re-precipitation from methanol/ether/acetone (1:4:5, 20 ml). $^1$H n.m.r. {500 MHz, $D_2O$}: $\partial$ 9.11, br d, *J* 3.4 Hz, 2H, H6, H6"; 8.32, t, *J* 8.1 Hz, 1H, H4'; 8.25, m, 2H, H4, H4"; 8.12, d, *J* 8.1 Hz, 2H, H3', H5'; 8.07, d, *J* 7.9 Hz, 2H, H3, H3"; 7.68, m, 2H, H5, H5"; 4.42, d, *J* 8.7 Hz, 1H, Ha; 3.71, d, *J* 11.6 Hz, 1H, either Hc or Hd; 3.51, dd, *J* 5.5, 11.9 Hz, 1H, either Hc or Hd; 3.35-3.23, m, 4H, Hx, Hy, Hb, He. ESMS (1:1 MeOH:$H_2O$, CV=30V): *m/z* 623.5 ($M^+$, 97%).

*Results*

*Antiprotozoal Activity*

2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) shows a wide range of antiprotozoal activity (Table 1). Against *Leishmania donovani* it has $ED_{50} = 3\mu M$ which is comparable with complexes with the best leaving groups, namely water or ammonia in the aqua- and ammine-2,2':6',2"-terpyridine-platinum(II) complexes respectively. This suggests that either intercalation into DNA is the mechanism of antiprotozoal action of this complex or that there is an enzyme which is inhibited by it. 2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II)(**1**) is even more effective against *Trypanosoma cruzi* and *Trypanosoma brucei*. 2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) is likely to have low toxicity towards mammalian cells. 2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) was tested *in vivo* in BALB/c mice challenged with *Leishmania donovani*. Six days post infection (**1**) was administered intra-peritoneally at 50mg/kg per day for five days which lead to 39% inhibition compared with the control group of mice. All the mice survived this regime.

Trypanothione reductase is an FAD-dependent enzyme which catalyses the reduction of trypanothione using NADPH as co-factor. The enzyme is found in the haemflagellate protozoa from the genera *Trypanosoma* and *Leishmania* and is a known target for drugs against these parasites. 2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) reversibly inhibits trypanothione reductase from *Trypanosoma cruzi* in the absence of NADPH with $K_i=60\mu M$ at pH 7.5. The enzyme (3nM), however, is 95% inactivated in 20 min. by 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) ($40\mu M$) in the presence of NADPH ($20\mu M$). From a full kinetic analysis the second order rate constant for irreversible inhibition, $k_i = 50\ M^{-1}s^{-1}$. From these observations is would seem that irreversible inactivation occurs by platination of the active site thiol group of Cys-52 generated from the Cys-52-Cys-63 disulphide bridge in the presence of NADPH.

Another possible target for 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) inhibition is tryparedoxin a thioredoxin-like protein found in trypanosomes which with trypanothione is an effective reductant of trypanosomal ribonucleotide reductase an enzyme required for the biosynthesis of deoxyribonucleotides in trypanosomes.

In the light of the above considerations further 2,2':6',2"-terpyridine-platinum(II) complexes have been investigated and the data for (**2**) and (**3**) shown in Table 1. It is clear from these results that thiolate-2,2':6',2"-terpyridine-platinum(II) complexes have considerable potential as antiprotozoal agents.

***Antirheumatoid Arthritic Activity***

Human thioredoxin reductase is now considered to be the site of action of organogold compounds such as aurothioglucose (S. Gromer *et al.*, *J. Biol. Chem.*, **1998**, *273*, 20096-20101) and auranofin which are used in the treatment of rheumatoid arthritis. Thus the thiolato-2,2':6',2"-terpyridine-platinum(II) complexes are likely to be agents useful in the treatment of rheumatoid arthritis. The 2,2':6',2"-terpyridine-platinum(II) analogue of aurothioglucose, i.e. (**4**) has been prepared and at 20$\mu$M concentration irreversibly inhibits human thioredoxin reductase within 10 min. in the presence of NADPH.

Human thioredoxin reductase is a homodimeric FAD-dependent enzyme and has been recently shown to be a seleno-enzyme. Only two other mammalian enzymes are known to contain selenocysteine, namely, glutathione peroxidases and thyroxine deiodinases. The selenocysteine forms a seleno-sulphide bridge at the active site analogous to the many disulphide oxidoreductases. In its reduced form the enzyme is inhibited by organic gold compounds (e.g. auranofin) used in the treatment of rheumatoid arthritis. Since selenocysteine is sufficiently nucleophilic to displace thiols from 2,2':6',2"-terpyridine-platinum(II) complexes, this is likely to be the site of platination by 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) and other thiolate-2,2':6',2'-terpyridine Pt(II) complexes, e.g. (**2**) and (**3**) leading

to the inactivation human thioredoxin reductase. Thus 2,2':6',2"-terpyridine-platinum(II) thiolate complexes are possible candidates for the treatment of rheumatoid arthritis.

*Antitumour Activity*

2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) is shown to possess antitumour activity against a number of human ovarian tumour cell lines (Table 2). However, displacement of the hydroxyethanethiol ligand by a nuclear base to form a covalent link with DNA has been shown not to occur (M. Howe-Grant *et al.*, *Biochemistry*, **1976**, *15*, 4339-4346). Intercalation into DNA is a possible mechanism of action but platination of an enzyme is also probable. Although 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) is more effective than carboplatin against some tumour cell lines, e.g. CH1cis$^R$, A2780, A2780cis$^R$ and SKOV-3, it is less effective than cisplatin and 2,2':6',2"-terpyridine-platinum(II) complexes with better leaving groups as the fourth ligand, which are known to be capable of platinating guanine residues in DNA. Nevertheless carboplatin is currently the agent of choice for the treatment of women with ovarian cancer.

It was considered that the antitumour activity of 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) could be due in part to its inhibition of human thioredoxin reductase. Thioredoxin is a small protein which in its reduced state is the specific reductant in the conversion of ribonucleotides to 2'-deoxyribonucleotides by ribonucleotide reductase. As such it is essential for the generation in eukaryotes of the 2'-deoxyribonucleotides required for DNA synthesis. This hypothesis has been tested. Initially it was shown that human thioredoxin reductase in the presence of NADPH was virtually completely inactivated in 10 min. by 20 $\mu$M 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**). Since human thioredoxin reductase contains the rare selenocysteine residue in its active site, it is likely that this is the site of platination. In the oxidised enzyme this residue is cross-linked with a cysteine, accounting for the failure of (**1**) to irreversibly inhibit the enzyme in the absence of NADPH. A number of thiolate

2,2':6',2"-terpyridine platinum (II) complexes have been investigated. The thiolate 2,2':6',2"-terpyridine platinum (II) complexes (**2**), (**3**) and (**4**), each at a concentration 20$\mu$M irreversibly inhibited human thioredoxin reductase within 10 min. in the presence of NADPH.

It was considered that the biological activity may correlate with the leaving ability of the thiolate ligand which should be linked to the pKa of the thiol. When 2-mercaptopyridine and 4-mercaptopyridine were incorporated as the fourth ligand in 2,2':6',2"-terpyridine-platinum(II) complexes, sulphur (as expected) was the prefered ligand giving the thiolate 2,2':6',2"-terpyridine-platinum(II) complexes. Similarly 2-mercapto-pyrimidine gave thiolate 2,2':6',2"-terpyridine-platinum(II) complex. When 2-mercapto-imidazole or 2-mercaptobenzimidazole were used, however, bis-platinum complexes were formed. This can be rationalised by postulating that the initial site of platination is at sulphur but that the close proximity of the positive charge on platinum to the NH group so lowers it pKa that it loses a proton and the negatively charge nitrogen is then rapidly platinated to give the bis-platinated product. The bis-platinated complexes are interesting as antitumour agents as they may have the ability to intercalate into DNA through the thiolate 2,2':6',2"-terpyridine-platinum(II) complex and platinate DNA through the second platinum complex. The possibility of using thiols with a wide range of $pK_a$s, differing charge and lipophilicity as the fourth ligand in 2,2':6',2"-terpyridine-platinum(II) complexes may make it possible to modulate the biological activity of these systems. Thus dithiophosphate O,O-diesters have low pKa values and their hydrophobicity may be controlled by the nature of the ester groups. The 2,2':6',2"-terpyridine-platinum(II) complexes retain a single positive charge. If thiosulphate is used as the fourth ligand, the complex becomes overall neutral and may more rapidly pass through cell membranes.

**Table 1**
***In vitro* Antiprotozoal Activity of (1), (2) and (3)**

| | | % Inhibition at concentrations in $\mu$g/ml | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 30 | 10 | 3 | 1 | 0.3 | 0.1 | 0.03 | 0.01 | $ED_{50}$($\mu$g/ml) |
| (1) | *L.donovani* | 99.8 | 99.3 | 63.3 | 0 | | | | | 3.05 |
| | *T.cruzi* | t/100 | t/100 | t/100 | 90.8 | 66.1 | 38.9 | | | 0.15 |
| | *T.brucei* | 100 | 100 | 100 | 100 | 100 | 100 | 66.3 | 35.9 | 0.02 |
| (2) | *L.donovani* | t/100 | 98.5 | 86.6 | 2.3 | | | | | 2.31 |
| | *T.cruzi* | t/+ | t/+ | t/+ | 64.9 | 60.3 | 32.6 | | | 0.25 |
| | *T.brucei* | 100 | 100 | 100 | 100 | 100 | 100 | 84.3 | 17.4 | 0.02 |
| (3) | *L. donovani* | t/100 | t/100 | t/100 | 98.5 | | | | | |
| | *T.cruzi* | t/100 | t/100 | t/100 | 88.7 | 77.4 | 58.6 | | | <0.1 |
| | *T.brucei* | 100 | 100 | 100 | 100 | 100 | 100 | 20.4 | 0 | 0.03 |

| Controls | | |
|---|---|---|
| Pentostam | *L.donovani* | 6.16$\mu$g$Sb^v$/ml |
| Benzimidazole | *T.cruzi* | 7.45 $\mu$g/ml |
| Pentamidine | *T.brucei* | 100% at 1$\mu$g/ml |

t/100 = toxic to macrophages, no parasites present
t/+ = toxic to macrophages, parasites present

**Table 2**

**The 96 hour $IC_{50}$ values in ($\mu$M) for the *in vitro* growth inhibition of human ovarian cell lines for (1) compared with carboplatin**

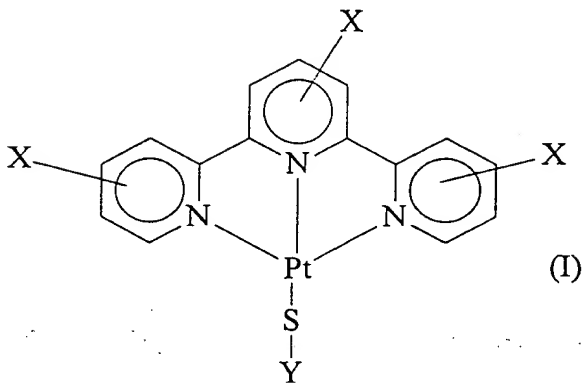
Two of the cell lines are resistant to cisplatin and one to doxorubicin

RF is the resistance factor: $IC_{50}$ resistant line/$IC_{50}$ parent line

| Compound | CH1 | CH1cis$^R$ | RF | CH1dox$^R$ | RF | A2780 | A2780cis$^R$ | RF | SKOV-3 |
|---|---|---|---|---|---|---|---|---|---|
| (1) | 14 | 12.5 | 0.9 | 11.5 | 0.8 | 18 | 20 | 1.1 | 18 |
| Carboplatin | 6.2 | 14.0 | 2.3 | — | — | 35 | >100 | — | >100 |

## CLAIMS

1. A compound which is a complex of formula (I)




(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

2. A compound as claimed in claim 1 wherein X is hydrogen, halogen or alkoxyl.

3. A compound as claimed in claim 1 or 2 wherein X is hydrogen, chlorine, methoxyl, ethoxyl or propoxyl.

4. A compound as claimed in any one of claims 1 to 3 wherein Y is alkyl, alkaryl, heterocyclyl or an inorganic oxyacid or inorganic oxyacid derivative.

5. A compound as claimed in any one of the preceding claims wherein Y is $(CH_2)_nOH$ or $(CH_2)_n NH_3^+$ wherein n is an integer of 1 to 6; $CH_2$aryl; a 5- or 6-membered saturated heterocyclic ring or a 5- or 6-membered unsaturated heterocyclic ring containing at least one N which may be fused to a 6-membered aryl ring; or $SO_3R$ or $PO_3R_2$ wherein R is hydrogen or alkyl.

6. A compound as claimed in claim 5 wherein n is an integer of at least 3.

7. A compound as claimed in any one of claims 1 to 5 which is

2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

2-aminoethanethiolate-(2,2':6',2"-terpyridine)platinum (II),

pyridine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),

pyridine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

pyridine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

pyridine-4-thiolate-(2,2':6',2"-terpyridine)platinum (II),

pyridine-4-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

pyridine-4-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

pyrimidine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),

pyrimidine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

pyrimidine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

imidazole-2-thiolate-bis(2,2':6',2"-terpyridine)platinum (II),

imidazole-2-thiolate-bis(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

imidazole-2-thiolate-bis(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

benzimidazole-2-thiolate-bis(2,2':6',2"-terpyridine)platinum (II),

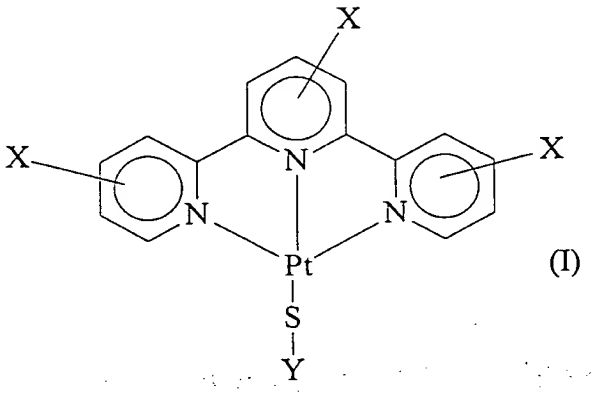
benzimidazole-2-thiolate-bis(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

benzimidazole-2-thiolate-bis(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II), or

1-thio-$\beta$-D-glucose(2,2':6',2"-terpyridine)platinum (II).

8. Use of a compound as defined in any one of the preceding claims in the manufacture of a medicament for use as an anti-protozoal, anti-rheumatoid arthritic or anti-tumour agent.

9. A compound which is a complex of formula (I)




(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or

oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

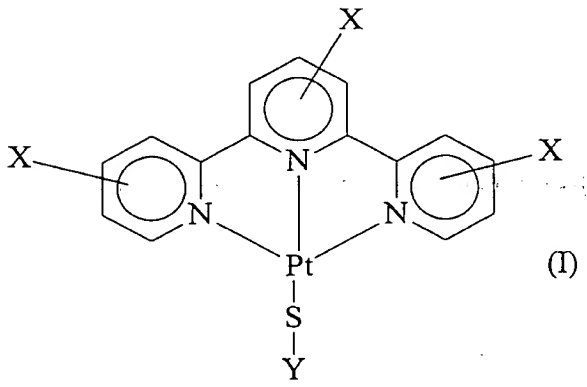
a pharmaceutically acceptable salt thereof, with the proviso that the complex of formula (I) is not 2-hydroxyethanethiolate(2,2':6',2"-terpyridine)platinum (II) or 2-aminoethanethiolate(2,2':6',2"-terpyridine)platinum (II).

10. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 7 or 9 in association with a pharmaceutically acceptable carrier or excipient.

## ABSTRACT

## PLATINUM (II) COMPOUNDS

A compound which is a complex of formula (I)



(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species;

or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.